UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,234	10/22/2001	Maria Marino	214038US0PCT	2544

22850 7590 02/24/2004

OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,234	MARINO ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4-7 and 10* is/are allowable.

6)☒ Claim(s) *3,8,9 and 13* is/are rejected.

7)☒ Claim(s) *1,2,11 and 12* is/are objected to.

8)☒ Claim(s) *1-13* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment and/or Claims

The amendment of 09 September 2003 has been entered in full. Claims 1-3 are amended and claims 4-13 are added.

Claims 1-13 are under consideration in the instant application. However, claims 1-13 will only be examined to the extent that they read upon SEQ ID NO: 1 (see election of 20 March 2003). The amino acid sequences of SEQ ID NOs: 1-4 are composed of different amino acids and are structurally and functionally unrelated to one another. Applicant contends that SEQ ID NOs: 3 and 4 are the reverse of SEQ ID NOs: 1 and 2 and are therefore related (pg 13 of the response of 09 September 2003). However, each of SEQ ID NOs: 1-4 is a unique sequence, requiring a unique search of the prior art. Searching all of the sequences in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

Applicant's continued traversal of the Restriction requirement set forth in the Paper of (28 January 2003) appears moot since the restriction requirement was made final in the previous Office Action (09 June 2003). If Applicant wishes to pursue the matter further, a petition should be filed in accordance with 37 CFR 1.144.

Withdrawn Objections/Rejections

1. The objections to claims 1-3 as set forth at pg 3 of the previous Office Action (09 June 2003) are *withdrawn in part* in view of the amended claims (09 September 2003). Please see claim objections, below.

Information Disclosure Statement

2. The two references submitted by Applicant with the response of 09 September 2003 have been received and considered by the examiner (Marino et al. and Brocke et al.). However, Applicant must submit a new PTO-1449 form that lists these references for the Examiner to sign and date (see MPEP § 609 and 37 CFR 1.98).

Claim Objections

3. Claims 1-3 and 8-13 are objected to because of the following informalities:

3a. Claims 1-3 and 8-13 recite non-elected SEQ ID NOs. The basis for this objection is set forth for claims 1-3 at pg 3 of the previous Office Action (09 June 2003).

Applicant's arguments as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant maintains that there is a unity of invention among the four claimed peptide sequences.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed above, the amino acid sequences of SEQ ID NOs: 1-4 are composed of different amino acids and are structurally and functionally unrelated to one another. Although SEQ ID NOs: 3-4 may be the reverse of SEQ ID NOs: 1-2, each of one of these sequences is a unique amino acid sequence, requiring a unique search of the prior art. Searching all of the sequences in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

Claim Rejections-35 USC § 112, first paragraph

4. Claims 3, 8-9, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth for claim 3 at pg 4-6 of the previous Office Action (09 June 2003).

The claims are directed to a method of treating a patient suffering from Multiple Sclerosis, said method comprising administering to a patient in need thereof an effective amount of a peptide compound comprising R-Asn-Gly-Val-Gly-His-Gly-Phe-Gly-Asn-Gly-Val-Gly-Pro-Gly-Thr-Gly-Pro-Gly-Ser-Gly-R' (SEQ ID NO: 1) where R is H- or $COCH_3$ and R' is COOH or $CONH_2$ and each amino acid has the D or L conformation. The claims recite that 1 to 100 mg/kg/day of the peptide compound is administered to a subject. The claims also recite a method of preventing the onset of multiple sclerosis in a human comprising administering to a patient an effective amount of a peptide compound having the sequence of R-Asn-Gly-Val-Gly-His-Gly-Phe-Gly-Asn-Gly-Val-Gly-Pro-Gly-Thr-Gly-Pro-Gly-Ser-Gly-R' (SEQ ID NO: 1) where R is H- or $COCH_3$ and R' is COOH or $CONH_2$ and each amino acid has the D or L conformation.

Applicant's arguments (09 September 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that it is clear from the discussion of relevant prior art in the text of the application that no undue burden for experimentation exists. Applicant argues that one of skill in the art, having the disclosure of the present specification in hand which indicates the efficiency of two peptide embodiments of the invention in the prevention of the onset of EAE in test mice,

would have no difficulty in implementing clinical treatment of human beings suffering from multiple sclerosis using these peptides. Applicant contends that the specification provides disclosure as to forms in which the peptide embodiments can be administered to the human being and administered amounts that would be useful in effectively treating a subject. Applicant indicates that in Karin et al. (J Exp Med 180(6): 2227-2237, 1998), for example, the authors state on pg 2235 that based on the test results of the incidence of the onset of EAE in test rats, clinical trials were conducted involving the administration of MBP.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action (09 September 2003), the specification only discloses that the *inducement of EAE* can be prevented by vaccination with the peptide of formula I (SEQ ID NO: 1). The specification does not teach treating any subjects already suffering from EAE by administration of the peptide of SEQ ID NO: 1, as required by the claims. Specifically, the specification teaches that two groups of mice are first immunized intraperitoneally with the peptide compound of formula I or II (pg 11, lines 1-5). The specification further discloses that after 2 weeks, EAE is induced all groups (including control) by challenge with P81-100 and mice are observed daily for clinical signs of EAE (pg 11, lines 8-22).

Therefore, undue experimentation would still be required of the skilled artisan to treat a subject or patient *already suffering* from Multiple Sclerosis (MS) by administering to the patient the peptide of SEQ ID NO: 1. A large quantity of experimentation would be required by one skilled in the art to determine the optimal dosage, duration, and route of administration of the peptide of SEQ ID NO: 1 for treatment of MS. The experiment in the specification is merely an invitation to the artisan to use the current invention as a starting point for further

experimentation. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". The specification outlines a prophetic procedure for treating a patient already suffering from multiple sclerosis. However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily treat multiple sclerosis in a patient.

Furthermore, Karin et al. teach that their MBP peptide p87-99[91K>A] prevents and reverses EAE in rats (abstract; pg 2230-2233; Tables 2-3; Figure 6). Karin et al. also indicate that clinical trials involving the administration of MBP have been undertaken in patients with MS (pg 2235, col 2). However, there is a difference between the results obtained by Karin et al. and the experiment disclosed in the specification of the instant application. Karin et al. observe that peptide p87-99[91K>A] not only prevents EAE but also reverses EAE in rats who manifest the disease. Conversely, the assay of the instant application only indicates that the peptide of SEQ ID NO: 1 is able to prevent EAE (pg 10-12). There are no methods or working examples that teach the peptide of SEQ ID NO: 1 is capable of treating EAE in animals or MS in humans who already display symptoms of the disease.

(ii) Applicant argues that the Examiner's comments concerning the necessity of submitting clinical trial results on human beings in order to demonstrate enablement are unfounded because clinical trials imply and require the disclosure of the drug(s) being tested which means that the identity of the drug(s) is (are) compromised. Applicant asserts that in the present application, the

in vivo assay of a drug on a susceptible strain of mice that is known to develop experimental autoimmune encephalomyelitis (assay 1) is a murine model of MS which is known to be predictive of the activity of a drug in man.

Applicant's arguments have been fully considered but are not found to be persuasive. It is not clear to the Examiner what clinical trial comments Applicant is referring to. The Examiner did not indicate that clinical trials on human beings had to be submitted to demonstrate enablement. However, the Examiner cited Wiendl et al. (BioDrugs 16(3): 183-200, 2002) in the previous Office Action (09 June 2003) as an indication of the state of the art at the time the invention was made. Wiendl et al. review MS trials that failed or were discontinued, including cytokine modulators, immunosuppressive agents, and T cell and T-cell receptor therapies, among others. Wiendl et al. indicate that theoretically promising agents may increase disease activity (such as lenercept and infliximab) or may be associated with unforeseen adverse effects (roquinimex) (pg 197, ¶ 3). Wiendel et al. also disclose that short-term favorable trends may reverse with prolonged follow-up. Therefore, the state of the art is such that not all MS therapeutic treatments are successful. Regarding the instant case, the experiment in the instant application only teaches that the peptide of SEQ ID NO: 1 prevents the onset of EAE. Undue experimentation would be required by the skilled artisan to determine the optimal dosage, duration, and route of administration of the peptide of SEQ ID NO: 1 for treatment of EAE/MS in subjects manifesting the disease. Although administration of the peptide of SEQ ID NO: 1 is able to prevent the onset of EAE, the skilled artisan cannot predict that the peptide of SEQ ID NO: 1 will also treat EAE/MS in any subject (rat or human), as evidenced by the failed experiments cited by Wiendl et al.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine the optimal dosage, duration, and route of administration of the peptide of interest and to treat a patient *suffering from MS* by administering the peptide of SEQ ID NO: 1, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of the administration of the peptide of SEQ ID NO: 1 to a patient already suffering from MS, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

Claims 4-7 and 10 are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
19 February 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER